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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,508	09/12/2005	Jonathan Alexander Terrett	2543-1-038PCT/US	2562

23565 7590 06/27/2007

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
06/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,508	TERRETT, JONATHAN ALEXANDER	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,16-23 and 25-27* is/are pending in the application.

4a) Of the above claim(s) *1-10,16-23 and 25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed 05/04/07 in response to the Office Action of 04/02/07 is acknowledged and has been entered.

Applicant's election with traverse of Group 8 claim 11 is acknowledged. The traversal is on the ground(s) that a search and examination of all of the inventions would not impose a serious burden on the examiner. Although applicant argues that search of Group 5 drawn to a method for the prophylaxis/and treatment of cancer comprising administering a polypeptide would require the search of identical classes as Group 8 and could also be searched without a serious burden of search, burden of search is not the criteria for proper restriction under PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d). Given that the inventions lack unity, for the reasons set in the Office Action of April 2, 2007, the restriction requirement is deemed to be proper and is therefore made FINAL.

2. Claims 1-11, 16-23, and 25-27 are pending.

3 Claims 1-10, 16-23, and 25-27 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

4. Claim 11 is currently under consideration.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

6. Claim 11 is objected to for containing subject material that is drawn to a non-elected invention. The claim recites "an antibody as defined in claim 6", which is a non-elected claim.

Amendments of the claims to include all of the limitations of an antibody as defined in claim 6 and to delete referenced claim 6 would obviate the rejection. Appropriate correction is required.

Specification

7. The disclosure is objected to because of the following informalities:

There are hyperlinks in the specification at p. 30, lines 40 and 41, and p. 31, line 1. Removal of the "http://" will disable the hyperlink and obviate this objection.

The brief description of Figure 1 is objected to for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs. As reference to the SEQ ID NOs: can be found elsewhere in the specification and the sequence listing has been filed , insertion of the appropriate SEQ ID NOs: in to the brief description of Figure 1 will obviate this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in

Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer in a subject, which comprises administering to said subject a therapeutically effective amount of an antibody as defined in claim 6.

The specification teaches that NKCC1, which is shown in Figure 1, SEQ ID NO: 1, is a bumetanide sensitive sodium-potassiumchloride (Na-K-Cl) cotransporter, see p.1 lines 37-39. The specification teaches that NKCC1 protein was isolated from a breast and pancreatic cancer cell line, see Example 1. NKCC1 mRNA was found to be expressed in normal mammary, prostate, testis and brain tissues and it was found that NKCC1 mRNA was overexpressed in breast and pancreatic tumor tissue, see Example 2 and Figs. 3 and 4. The specification teaches that immunostaining with an antibody to NKCC1 showed that NKCC 1 is specifically and highly expressed in the ductal carcinoma cells of the breast cancer tissue compared with adjacent breast tissue, see Example 3. The specification teaches immunostaining for NKCC1 showed increased staining for NKCC1 in both lung and pancreatic cancer tissue sections compared to adjacent control sections, see Example 3.

One cannot extrapolated the teachings of the specification to the enablement of the claims because no nexus has been established between the prophylaxis and/or treatment of breast, lung, and/or pancreatic cancer and administering to a subject an antibody that specifically binds to NKCC1 because 1) it is well known in the art that the development of anticancer therapeutics is unpredictable and the refractory nature of cancer to drugs is well known in the art and 2) it is well known in the art that the prevention of disease, particularly cancer, is unpredictable.

1) It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that it was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that

has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Because of the known unpredictability of the cancer therapeutic art and in particular the antibody therapeutic cancer therapeutic art, no one of ordinary skill in the art would believe it more likely than not that the claimed invention will function as claimed with a reasonable expectation of success based only on the in vitro binding assays exemplified in the specification.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of *in vivo* experimental evidence, no one skilled in the art would believe it more likely than not that an antibody that specifically binds to NKCC1 would function as anti-cancer antibody. In addition, anti-tumor antibodies must

accomplish several tasks to be effective. They must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the antibody. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the antibody. In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. Given the above, based only on the in vitro binding studies exemplified no one skilled in the art would believe it more likely than not that an antibody that specifically binds to NKCC1 would function as an anti-cancer antibody or that the invention will function as claimed with a reasonable expectation of success. Thus one of skill in the art would be forced into undue experimentation to use the claimed invention.

2) As drawn to prevention, the term "prophylaxis" is defined as "Prevention of or protective treatment for disease" (see The American Heritage® Dictionary of the English Language: Fourth Edition. 2000, Fourth Ed., www.bartleby.com/61/8/P0600800.html). The specification lacks the critical steps necessary in presenting some type of predictable response in a population of hosts deemed necessary to prevent cancer or to protect against cancer. Reasonable guidance with respect to preventing or protecting against any cancer relies on quantitative analysis from defined

populations that have been successfully pre-screened and are predisposed to particular types of cancer or have had cancer. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which are not disclosed in the specification. Furthermore, with regards to the prevention of cancer in a mammal comprising administering an antibody, the specification does not disclose sufficient guidance or objective evidence that such antibodies would predictably prevent the formation of cancer cells in a mammal. In particular, as drawn to validating preventive therapeutics, Byers, T. (CA Journal, Vol. 49, No. 6, Nov/Dec. 1999) teaches that randomized controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, Byers suggests that chemo-preventitive trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably prevent the formation of tumors in a mammal. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed.

Given the above and given the absence of evidence in any appropriate model drawn to the treatment or prophylaxis of breast, lung, and/or pancreatic cancer in a subject with an antibody the specifically binds to NKCC1, one of skill in the would not believe it more likely than not that one of skill in the art could practice the claimed invention without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function

as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

9. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claim 11 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer in a subject, which comprises administering to said subject a therapeutically effective amount of an antibody that specifically binds to SEQ ID NO: 1, does not reasonably provide enablement for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer in a subject, which comprises administering to said subject a therapeutically effective amount of an antibody that specifically binds polypeptides comprising SEQ ID NO: 1 or specifically binds to the derivatives or fragments of SEQ ID NO: 1 claimed in claim 1b and 1c. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer in a subject, which comprises administering to said subject a therapeutically effective amount of an antibody as defined in claim 6, which encompasses antibodies that specifically binds to the derivates or fragments of SEQ ID NO: 1 claimed in claim 1b and 1c.

This means that administering an antibody any of derivates or fragments of SEQ ID NO: 1 claimed in claim 1b and 1c to a subject with breast, lung and/or pancreatic cancer will be predictably be effective for prophylaxis and/or treatment of said cancer.

The specification teaches as set forth above. The specification also teaches as drawn to the NKCC1 polypeptide claimed in 1b that alterations in the amino acid sequence of a protein can occur which do not affect the activity of a protein. These include amino acid deletions, insertions and substitutions and can result from alternative splicing and/or the presence of multiple translation start sites and stop sites, see p. 5, lines 21 to 26 . Further it is noted that claim 1b states that a derivative may have one or more amino acid substitutions, modifications , deletions, or insertions relative to the amino acid sequence in SEQ ID NO: 1 which retains the immunological **or** (emphasis added) biological activity of NKCC1. It is noted in particular, that no particular biological activity or immunological activity is defined either by the claim or by the specification as originally filed.

One cannot extrapolate the teachings to the scope of the claims because the specification has not established a nexus between all of the variant forms of NKCC1 contemplated and

claimed and the treatment or prophylaxis of breast, lung and/or pancreatic cancer. Furthermore, one of skill in the art could not predictably establish a nexus between all of the NKCC1 variants contemplated and claim and the the treatment or prophylaxis of breast, lung and/or pancreatic cancer because (1) there is insufficient guidance and direction as to how to make and use antibodies to all of the NKCC1 proteins contemplated and claimed because the encompass unknown antigens (2) the art of protein chemistry is unpredictable and even the alteration of a single amino acid in a polypeptide will often dramatically affect the biological activity and characteristics of that polypeptide and (3) the known unpredictability of determining the function or expression of one splice variant, derivative, or fragment of a given protein based on that of another splice variant, derivative, or fragment of a given protein.

(1) As drawn to claiming antibodies to unknown antigens, the courts have found that definition of an antibody by binding to an unknown is not enabling. In particular, the court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites En zo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently

described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

To reiterate, applicant is claiming antibodies against unknown derivatives of NKCC1 and unknown proteins that comprise SEQ ID NO: 1 and since an antibody is defined by its antigen binding capability, claims drawn to unknown antibodies that bind to unknown antigens are not enabled. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predictably make or use the broadly claimed antibodies with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

2) As drawn to all of the variant NKCC1 proteins contemplated and claimed predictably being associated with breast, lung, or pancreatic cancer, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in

turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results

underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411; 1st column, 4th paragraph). In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col. 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col. 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col. 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col. 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). The teachings of Bork are clearly illustrated by Pero et al. (US PG Pub 20030105000) who specifically teach on page 73 that the SH2 domain of Grb14 is 81% similar to the SH2 domain of Grb7 on the amino acid level, but

although Grb7 binds to ErbB2, Grb14 does not bind to ErbB2. Further, although the SH2 domain of Grb2 is only 50% similar to Grb 7 on the amino acid level, both Grb2 and Grb7 bind to the same site on ErbB2. Thus, sequence identity or similarity alone cannot be used to predict the function of a protein.

Given not only the teachings of Bowie et al, Lazar et al, Burgess et al, Scott et al. and Pero et al. but also the limitations and pitfalls of using computational sequence analysis taught by Bork clearly the ability of all of the variants of NKCC1 encompassed by the claims to be associated with breast, lung, or pancreatic cancer could not be predicted, based on structural similarity to SEQ ID NO: 1, respectively. Furthermore, given the above, one of skill in the art could not reliably predict that a method using antibodies to all of the variants of NKCC1 claimed would predictably treat or be useful for the prophylaxis of breast, lung, or pancreatic cancer. Given the above, it is clear that undue experimentation would be required of one of skill in the art to make and use a method for the treatment or prophylaxis of breast, lung, or pancreatic cancer with antibodies that bind to the full scope of NKCC1 proteins encompassed by the claims. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

2) As drawn to splice variants, there are many examples known in the art of differing expression and function between splice variants. In particular, Benedict et al (J. Exp. Medicine, 2001, 193(1) 89-99) specifically teach that two splice isoforms of terminal deoxynucleotide transferase (a long form and a short form) enter the nucleus but have different activity, the long form does not catalyze nontemplated nucleotide addition but rather modulates the activity of the short form (see abstract). Jiang et al (JBC, 2003,

278(7) 4763-4769) specifically teach that the type 3 Ca2+ release channel, RyR3 exhibits strikingly different pharmacologic and functional properties depending on the tissues in which it resides. Upon examination, seven tissue specific alternatively spliced variants of RyR3 were detected. One of the variants was unable to form a functional channel but was able to suppress the activity of a different release channel. The authors conclude that tissue-specific expression of RyR3 splice variants is likely to account for some of the pharmacologic and functional heterogeneities of RyR3 (see abstract). The abstract of Matsushita et al (FEBS Letters, 1999, Vol. 443, pp. 348-352) teaches that latrophilins exhibit alternative splicing resulting in latrophilin-1, which is present in brain and endocrine cells, latrophilin-2, which is ubiquitous, and latrophilin-3 which is brain-specific. The abstract of Singh et al (Glycobiology, 2001, Vol. 11, pp. 587-592) teach that the CD44 splice variant, CD44v, is the major PNA-binding glycoprotein in colon cancer cells in contrast to standard CD44. These references serve to demonstrate that one of skill in the art cannot anticipate the biological activity or tissue distribution of splice variants, derivatives, or fragments of a given protein based on the biological activity or tissue distribution of the wild-type protein or a single protein isoform.

Thus, it is clear that one could not reliably predict which of the claimed variants of the NKCC1 protein would be involved in the etiology or pathology of pancreatic, lung, or breast cancer or which would be an appropriate target for the treatment or prophylaxis of pancreatic, lung, or breast cancer so that the method of claim 11 would function as claimed. The specification provides neither information nor guidance on how to predictably identify which of the broadly claimed variants of the NKCC1 protein will be useful in the treatment or prophylaxis

of pancreatic, lung, or breast cancer. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention. Thus, undue experimentation would be required to make and use the invention as broadly claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has

been provided which would allow one of skill in the art to predict that the invention will function as contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

10. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method for the prophylaxis and/or treatment of breast, prostate, pancreatic, and/or colon cancer in a subject, which comprises administering to said subject a therapeutically affective amount of an antibody as defined in claim 6, which is an antibody that specifically binds to a polypeptide as defined in claim 1, an NKCCC1 polypeptide which: a) comprises or consist of the amino acid sequence shown in Figure 1 (SEQ ID NO:1); **b) is a derivative having one or more amino acid substitutions, deletions, or insertions relative to the amino acid sequence of shown in Figure 1 (SEQ ID NO:1); or c) is a fragment of a polypeptide having the sequence shown in Figure 1 which is at least ten amino acids long and has at least 70% sequence identity over the length of the fragment.**

The state of the art is such that it is well know in the art that protein biochemistry is unpredictable and, thus, predicting protein function from structure is unpredictable. In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry

out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen.

Given the above, it is clear that in the protein biochemistry arts an adequate written description is essential for one of skill in the art to recognize which of the claimed derivatives of NKCC1 are even associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the

written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the

written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer,

in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, nor does the specification provide any partial structure of such a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, nor any physical or chemical characteristics of a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses SEQ ID NO: 1, this does not provide a description of a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer that would satisfy the standard set out in Enzo.

The specification also fails to describe a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer by the test set out in Lilly. The specification describes only SEQ ID NO: 1. Therefore, it necessarily fails to describe a "representative number" of a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic

cancer. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description a derivative or fragment NKCC1/SEQ ID NO: 1 polypeptide that is associated with breast, lung and/or pancreatic cancer and would be an appropriate target for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer that is required to practice the claimed invention. Since the specification fails to adequately describe the products upon which the methods depend, it also fails to adequately describe their method of use.

11. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method for the prophylaxis and/or treatment of breast, prostate, pancreatic, and/or colon cancer in a subject, which comprises administering to said subject a therapeutically affective amount of an antibody as defined in claim 6, which is an antibody that specifically binds to a polypeptide as defined in claim 1, an NKCCC1 polypeptide which: a) **comprises** or consist of the amino acid sequence shown in Figure 1 (SEQ ID NO:1); **b) is a derivative having one or more amino acid substitutions, deletions, or insertions relative to the amino acid sequence of shown in Figure 1 (SEQ ID NO:1); or c) is a fragment of a polypeptide having the sequence shown in Figure 1 which is at least ten amino acids long and has at least 70% sequence identity over the length of the fragment.**

The state of the art is such that it is well know in the art that protein biochemistry is unpredictable and that protein binding interactions, such as antibody/antigen interactions, are sensitive to even minor changes in protein sequence, thus the ability of a given antibody to bind variant proteins is not predictable.

In particular, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257:1306-1310,) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid alterations are possible in any given protein, the position within the protein's sequence where such amino acid alterations can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative alterations or no alterations. The exquisite sensitivity of binding proteins to alterations of even a single amino acid is well known in the art. For example, Rudikoff et al, (PNAS, USA, 1982, 79: 1979) specifically teach that even minor changes in the amino acid sequence of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. In particular, Rudikoff et al teach that alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein results in the loss of antigen-binding function. Coleman et al. (Research in Immunology, 1994; 145(1): 33-36) teach single amino acid changes in an antigen can effectively abolish antibody antigen

binding. Furthermore, Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444, see abstract in particular) teach single amino acid substitutions outside the antigenic site on a protein affects antibody binding. Further, the sensitivity of binding proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. These references demonstrate that even a single amino acid alteration or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a binding protein/antigen-antibody interaction.

Thus, given the above, it is clear that in the antibody arts an adequate written description of the antigen is essential for one of skill in the art to make and use the claimed invention which depends on an antibody that specifically binds to the broadly claimed NKCC1 polypeptide of claim 1.

Given the broadly defined peptide of claim 1 to which the antibody of claim 6 specifically binds which includes unknown derivatives of NKCC1/SEQ ID NO: 1 and unknown proteins comprising SEQ ID NO: 1, it is evident that the specification does not provide a written description of the broadly claimed antibody that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer for the reasons set forth below.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the

written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the

written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of an antibody that specifically binds to the broadly claimed NKCC1 polypeptide of claim 1 that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe an antibody that binds to specifically broadly claimed NKCC1 polypeptide of claim 1 that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any

antibody that binds to specifically broadly claimed NKCC1 polypeptide of claim 1 that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, nor does the specification provide any partial structure of such an antibody, nor any physical or chemical characteristics of an antibody that specifically binds to the broadly claimed NKCC1 polypeptide of claim 1 that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses antibodies to SEQ ID NO: 1, this does not provide a description of antibodies that specifically bind to the broadly claimed NKCC1 polypeptide of claim 1 that are useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer that would satisfy the standard set out in Enzo.

The specification also fails to describe an antibody that specifically binds to the broadly claimed NKCC1 polypeptide of claim 1 that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer by the test set out in Lilly. The specification describes only antibodies to SEQ ID NO: 1. Therefore, it necessarily fails to describe a "representative number" of species antibodies that specifically bind the broadly claimed NKCC1 polypeptide of claim 1. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description an antibody that specifically binds to the broadly claimed NKCC1 polypeptide of claim 1 that is useful for a method for the prophylaxis and/or treatment of breast, lung and/or pancreatic cancer that is

required to practice the claimed invention. Since the specification fails to adequately describe the products upon which the methods depend, it also fails to adequately describe their method of use.

Further, given that the claims encompass an antibodies that bind to an unknown antigen, the following teaching of the court as set out in Noelle also clearly applies to the instant claimed invention. The court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J.*

Yellin (CAFC, 02-1187, 1/20/2004). To reiterate, applicant is claiming antibodies against unknown derivatives of NKCC1 and unknown proteins that comprise SEQ ID NO: 1 and since an antibody is defined by its antigen binding capability the specification does not provide an adequate written description of the claimed invention.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claim 11 is rejected under 35 U.S.C. 102(e) as being anticipated by Veiby US2003/0068636, June 27, 2001, as evidence by the alignment in Appendix 1.

Veiby et al. teach NKCC1 as SEQ ID NO: 74 which is 100% identical to SEQ ID NO: 1 of the instant invention. Veiby et al. teach antibodies to NKCC1 and treatment of breast cancer with therapeutic antibodies to NKCC1, see paragraphs [0186] and [0199] of the published application.

Information Disclosure Statement

12. The information disclosure statement filed April 5, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because a CD cannot be used to submit an IDS listing or copies of the documents cited in the IDS, see 609.04(a). It has been placed in the application file, but the information referred to therein that is lined out has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the

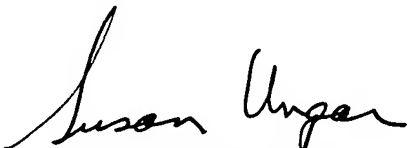
requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

13. No claim allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig
Examiner
Art Unit 1642

PJR

Appendix 1

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RESULT 1
US-10-176-847-74
; Sequence 74, Application US/10176847
; Publication No. US20030068636A1
; GENERAL INFORMATION:
;  APPLICANT: Veiby, Petter Ole
;  TITLE OF INVENTION: COMPOSITIONS, KITS, AND METHODS FOR
;  TITLE OF INVENTION:  IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF
BREAST
;  TITLE OF INVENTION:  AND OVARIAN CANCER
;  FILE REFERENCE: MRI-039
;  CURRENT APPLICATION NUMBER: US/10/176,847
;  CURRENT FILING DATE:  2002-06-21
;  NUMBER OF SEQ ID NOS: 112
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 74
;   LENGTH: 1212
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-176-847-74

  Query Match             100.0%;  Score 6227;  DB 4;  Length 1212;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 1212;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

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Qy        121 EASGESEPAKGSEEAKGRFRVNFVDPAASSSAEDSLSDAAGVGVDGPNVSFQNGGDTVLS 180
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Db        361 GPEFGGAIGLIFAFANAVAVAMYVVGFAETVVELLKEHSILMIDEINDIRIIGAITVVIL 420

Qy        421 LGISVAGMEWEAKAQIVLLVILLLAIGDFVIGTFIPLESKKPKGFFGYKSEIFNENFGPD 480
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Db        421 LGISVAGMEWEAKAQIVLLVILLLAIGDFVIGTFIPLESKKPKGFFGYKSEIFNENFGPD 480

Qy        481 FREEETFFSVFAIFFPAATGILAGANISGDLADPQSAIPKGTLLAILITTLVYVGIAVSV 540
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Qy       1021 KNTIDVWWLFDDGGLTLLIPYLLTTKKKWKDCKIRVFIGGKINRIDHDRRAMATLLSKFR
1080
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 KNTIDVWWLFDDGGLTLLIPYLLTTKKKWKDCKIRVFIGGKINRIDHDRRAMATLLSKFR
1080
```

```
Qy       1081 IDFSDIMVLGDINTKPKKENIIAFEEIIEPYRLHEDDKEQDIADKMKEDEPWRITDNELE
1140
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081 IDFSDIMVLGDINTKPKKENIIAFEEIIEPYRLHEDDKEQDIADKMKEDEPWRITDNELE
1140

Qy       1141 LYKTKTYRQIRLNELLKEHSSTANIIVMSLPVARKGAVSSALYMAWLEALSKDLPPILLV
1200
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1141 LYKTKTYRQIRLNELLKEHSSTANIIVMSLPVARKGAVSSALYMAWLEALSKDLPPILLV
1200

Qy       1201 RGNHQSVLTFYS 1212
             ||||||||||||
Db       1201 RGNHQSVLTFYS 1212
```